27.2

Stem cells versus chondrocytes for cartilage repair

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The current standard of clinical care for cartilage repair is microfracture especially for small, focal defects in the articular cartilage of the knee. The actual sequence of events and outcome of this procedure are understudied, considering the pervasive use of this technique. It is assumed that the microfracture produces a bleed and subsequent clot. It is imagined that Mesenchymal Stem Cells (MSCs) come up from the bottom (i.e., marrow) and contribute to the resulting tissue that replaces the clot. This repair tissue is firm on arthroscopic probing and is thought to be fibrous or fibro-cartilage (at best). In general, if successful, this procedure decreases pain, provides a smooth surface and lasts for several months to years. The expectation is that ultimately this fibrous tissue will fail and other operative approaches will be required. In a sense, microfracture may be a form of in vivo stem cell therapy. I would expect this to be highly successful in patients below the age of 10 and not successful above the age of 65.

The current use of tissue-engineered implants involves autologous chondrocytes in a defect either placed within a scaffold, or below a periosteum flap. The long-term success of these procedures are comparable to microfracture and some data suggest that these may be better because the defects are filled with more cartilage than fibrous tissue.

Several groups have provided data from preclinical models using chondrocytes (both allo- and autologous) and MSCs (both allo- and autologous) in cartilage repair/regeneration procedures. In all cases, the cells have been culture-expanded and combined with scaffolds of natural and/or man-made polymers. The expanded cells are clearly different from their in vivo counterparts and the issue is whether the redifferentiation or initial differentiation of these cells will produce the appropriate repair cartilage upon implantation.

The lecture will review research from the Skeletal Research Center and other labs on the comparisons between chondrocytes from various anatomic locations and MSCs. The challenge for the investigators who work with MSCs is to understand what sequential exposure pattern of bioactive factors is required to fabricate cartilage tissue that has the proper macromolecular composition and mechanical properties to be implanted into either chondral or osteochondral defects. Unresolved issues are how to control the differentiation and biosynthetic sequence to fabricate cartilage that is anatomical site specific. In addition, the stratification of molecular compounds from top to the bony bottom of cartilage will require additional control elements. Although the future expectations are very positive for these approaches, the challenges are currently quite high. Supported by grants from National Institutes of Health.

27.3

Clinical use of stem cells in cartilage repair.

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The purpose of this presentation is to review the types of stem cells in clinical application for cartilage repair, and the functional outcome associated with their use.

Manuscripts and clinical trials detailing the clinical implantation of stem cells for cartilage repair were reviewed.

There are very few reports of the clinical application of mesenchymal stem cells (MSC), and only animal studies of embryonic stem cells (ES) for cartilage regeneration despite the numerous manuscripts investigating mechanisms to enhance chondrogenic differentiation of ES or MSCs. Tissue engineering studies indicate that in order to restore the cartilage matrix and thereby the mechanical integrity of an articular cartilage defect, a cell source is needed to synthesize the extracellular matrix. However, the optimal cell type remains to be identified as either mature chondrocytes or stem cells; and if stem cells, the preferred tissue source would then need to be determined. It is also unclear if pluripotent stem cells, implanted in an articular cartilage or cartilage/bone defect, will spontaneously differentiate into chondrocytes, or if it is necessary to drive stem cells down a chondrogenic pathway prior to implantation. Another unresolved issue is the clinical importance of type X collagen synthesis by MSCs undergoing chondrogenesis in vitro. The concern is that these cells could continue onto hypertrophy and apoptosis.

Embryonic stem cells have not been used in clinical patients, and although studies in rodents are encouraging, is appears as through optimization of implantation protocols is important to avoid teratoma formation.1,2

Adult-derived stem cells from bone marrow, muscle, synovium, fat, periosteum, and the superficial zone of mature cartilage have been investigated in vitro for cartilage regeneration applications, but only bone marrow-derived MSCs have been used clinically. Although not an explicit MSC therapy, microfracture is thought to allow the ingress of MSCs from the underlying bone marrow. A distinct advantage of microfracture is its immediate availability for point-of-care application. Cartilage repair and restoration of joint function following microfracture has been investigated in horses3,4, humans5, and non-human primates6. Combined, these studies suggest that microfracture results in increased tissue volume and improved patient comfort and function compared to no treatment. However, repair tissue formed after microfracture remains deficient in key extracellular matrix components such as aggrecan and collagen type II. The repair tissue formed is deficient in critical matrix proteins and in many instances deteriorates, resulting in the return of clinical signs, within two years of the microfracture procedure. Another point-of-care MSC-based therapy is marketed under the trade name of Chondrogen (Osiris Therapeutic Inc.) and is in phase I/II clinical trials. Chondrogen is autologous MSCs injected into the joint capsule, and is primarily aimed at meniscus regeneration. An interim report released in February 2007, stated that Chondrogen did not increase meniscus volume, but in about 30% of patients "improvement in baseline cartilage and joint condition was noted in patients treated with the stem cell drug".

To increase the number of autogenous MSCs implanted in a cartilage defect as compared to microfracture, a study was performed where autogenous MSCs were propagated in tissue culture, and implanted in autogenous fibrin into full-thickness cartilage defects. The MSC/fibrin constructs lead to enhanced early chondrogenesis, but they did not significantly enhance the long-term histologic appearance or biochemical composition of full-thickness cartilage lesions.7 Our laboratory is presently working towards development of a patient-side method to concentrate stem cells in bone marrow using a specialized centrifugation technique. In addition to being a table-side technique, other advantages of such a bone marrow aspirate concentrate (BMAC) include the simultaneous concentration of platelets which serve as a reservoir for numerous chondrogenic growth factors, and the BMAC slurry can be implanted under arthroscopic guidance. This BMAC graft construct has been arthroscopically implanted into full-thickness cartilage defects in the equine lateral trochlear ridge and the 3T MRI images and tissues are presently being evaluated.

Studies investigating the chondrogenic potential of stem cells suggest that synthesis of a neocartilage matrix is possible using stem cells from a variety of tissue sources. Present clinical data suggests that MSCs do not fully repair articular cartilage defects. However, there are numerous variables including other types of